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Report from the Rockefellar Foundation Sponsored International Workshop on reducing mortality and improving quality of life in long-term survivors of Hodgkin's disease: July 9–16, 2003, Bellagio, Italy

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Abstract: A workshop, sponsored by the Rockefellar Foundation, was held between 9 to 16 July, 2003 to devise strategies to reduce mortality and improve quality of life of long-term survivors of Hodgkin's disease. Participants were selected for their clinical and research background on late effects after Hodgkin's disease therapy. Experts from both developed and developing nations were represented in the workshop, and efforts were made to ensure that the proposed strategies would be globally applicable whenever possible. The types of late complications, magnitude of the problem, contributing risk factors, methodology to assess the risk, and challenges faced by developing countries were presented. The main areas of late effects of Hodgkin's disease discussed were as follows: second malignancy, cardiac disease, infection, pulmonary dysfunction, endocrine abnormalities, and quality of life. This report summarizes the findings of the workshop, recommendations, and proposed research priorities in each of the above areas.

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Since the mid-1960s, Hodgkin's disease, a cancer of the lymph nodes that afflicts young people, has become highly curable. Because of advances in treatment, there are over 300 000 survivors of Hodgkin's disease in the United States, Canada, and Europe alone and many more survivors worldwide. Despite this success, it has become apparent that survivors of this disease are at significantly increased risk of dying from the late effects of treatment (1–4). Second cancers and cardiac disease often develop in these patients 10–25 yr or more after treatment – usually as patients enter middle age. Currently, there are few comprehensive guidelines available for the management of patients cured of Hodgkin's disease.

A workshop, supported by the Rockefellar Foundation, was held from 9 to 16 July 2003 to devise strategies to reduce mortality and improve

quality of life in long-term survivors of Hodgkin's disease. A tandem objective was to generate interchange from developed and underdeveloped countries so that the devised strategies would be globally applicable whenever possible. This paper reports the findings and recommendations of the workshop.

Participants and structure of the workshop

The following physicians participated in the workshop: Peter Mauch (Boston, MA, USA), Andrea Ng (Boston, MA, USA), Berthe Aleman (Amsterdam, The Netherlands), Patrice Carde (Paris, France), Louis Constine (Rochester, NY, USA), Volker Diehl (Cologne, Germany), Ketayun Dinshaw (Mumbai, India), Mary Gospodarowicz (Toronto, Canada), Steve Hancock (Stanford, CA, USA), David Hodgson (Toronto, Canada), Richard Hoppe (Stanford, CA, USA), Raymond Liang (Hong Kong), Markus Loeffler (Leipzig, Germany), Lena Specht (Copenhagen, Denmark), Lois B. Travis (Bethesda, MD, USA), Andrew Wirth (Melbourne, Australia), Joachim Yahalom (New York, NY, USA). Participants were selected for their expertise in the late consequences of treatment for Hodgkin's disease.

A detailed program with preliminary information was provided to the participants prior to the meeting. Participants were selected to represent both developed and developing nations from the fields of cardiology, epidemiology, statistics, health care delivery, and oncology, and asked to prepare presentations for the workshop based on their experience and expertise. Three large cooperative groups, The European Organization for Research and Treatment of Cancer (EORTC) and the German Hodgkin's Study Group (GHSG), and the Children's Oncology Group, organizations that have had a research interest in identifying risk factors for the late effects of treatment, were represented. Physicians from Asia, Australia, Europe, and North America participated. The presentations were sent to all participants prior to the meeting. The first 3 d of the workshop focused on a comprehensive review of pertinent data published in peer-reviewed clinical journals as well as recent unpublished data. This information was then utilized in the working groups held during the last 3 d.

Current institutional and cooperative group data were presented on excess mortality, on the excess incidence of cardiac disease and second malignancy, and on decreased health-related quality of life in survivors of Hodgkin's disease. Data were reviewed for patients followed out to 30 yr after Hodgkin's disease. We identified prognostic factors for the development of late morbidity and mortality; these included both treatment-related risk factors (i.e. type and extent of chemotherapy and radiation therapy) and patient-related factors (i.e. age at treatment, genetic history, tobacco). Enumeration of treatment-related and patient-related factors were identified to aid in developing research proposals and devising evidence-based clinical guidelines for the long-term follow-up of survivors of Hodgkin's disease. Specific prevention and early detection strategies based on risk were outlined at the workshop.

Data were presented on differences in staging, treatment and prognosis of patients with Hodgkin's disease in developing countries. Challenges to the delivery of health-care in developing countries were discussed with specific data presented from India, China, and Central America. Data from Australia also provided for identification of differences compared to Europe and North America.

Four working groups were held the last 3 d of the workshop. Group leaders were assigned for each of the following three areas: second malignancy, cardiac dysfunction, and other effects (including loss of fertility, thyroid, pulmonary, and infectious complications) after Hodgkin's disease. The fourth working group evaluated further reduction in initial treatment as a means to reduce treatment-related complications. The working groups identified the following general areas where additional research is needed:

(i) Continued ongoing research (risk prediction, risk reduction, managing survivors through screening, prevention and treatment, research priorities, research methods, research partnerships, and research in developing countries).
(ii) Recommendations for current clinical practice (follow-up studies, screening, and prevention).
(iii) Improving the education of physicians and patients.

Results

Second malignancies

Summary of data presented: The contribution of second malignancies to the excess mortality of survivors of Hodgkin's disease, the incidence, types and temporal trends of, and risk factors for second malignancies, were reviewed. Data from single- and multiple-institution databases (Stanford, Harvard, University of Rochester, The Netherland and Rotterdam Cancer Centers, Cochrane Haematological Malignancies Group), and from population-based cancer registries (Ontario Cancer Registry, Surveillance, Epidemiology and End Results [SEER] Program, and the nationwide registries in

Denmark, Finland, and Sweden) were presented (2–7). Several consistent findings emerged as follows:

(i) Second malignancy represents the leading cause of death in long-term survivors of Hodgkin's disease, and the risk appears to increase with increasing follow-up time at least out to 20–25 yr after Hodgkin's disease.
(ii) Solid tumors represent the majority of cases of second malignancies after Hodgkin's disease, most of which occur after a minimal latency of 5–10 yr.
(iii) Breast cancers and lung cancers account for the largest absolute excess risk of solid tumors.
(iv) Risk factors for breast cancer include young age at chest irradiation (age < 30–35), and increasing dose of radiation, whereas premature menopause due to treatment has a protective effect.
(v) Risk factors for lung cancer include chest irradiation (dose-related), alkylating agent chemotherapy (dose-related) and smoking (multiplicative effect with treatment exposure).
(vi) Data suggest that more modern treatment (safer chemotherapy, smaller radiation fields and lower doses of radiation) are associated with less risk of developing a second malignancy.

Extensive information is available documenting and characterizing the risk of second malignancies after Hodgkin's disease. Potential interventions include implementation of prevention and early detection programs targeted at survivors identified to be at high risk. However, there is a paucity of data establishing the effectiveness of these strategies. Barriers to prospectively evaluating prevention and screening programs for second malignancies include the relatively small number of long-term survivors available within each cancer center, difficulty in tracking eligible subjects, as well as the competing morbidity in these patients.

The results of a feasibility study conducted at the Dana-Farber Cancer Institute on the use of tamoxifen as chemoprevention in young women who received mantle irradiation for Hodgkin's disease were presented (8). A disappointingly low enrollment rate of only 11.5% in this pilot study led to the conclusion that a randomized trial addressing this question is unlikely to be feasible. Concern with side effects of tamoxifen was one of the most frequently quoted reasons for opting out of the study. A decision and cost-effectiveness analysis study was also presented looking at the role of tamoxifen in the same population (9). The use of Markov modeling to simulate a clinical trial bypasses the problem of poor accrual and lack of statistical power, but limitations of this approach include the need to make simplifying assumptions in the modeling of the clinical course, and the uncertainties of the estimates used in the model. Extrapolating data from the normal population (10), and assuming similar efficacy in breast cancer risk reduction, this analysis showed that the use of tamoxifen in women after Hodgkin's disease therapy was cost-effective and resulted in a survival gain that was within the range of a number of well-accepted oncological interventional strategies.

There are only limited prospective data on the role of screening for the detection of second malignancies in survivors of Hodgkin's disease. Whether screening mammography improves survival in women treated for Hodgkin's disease has not been formally evaluated. Several studies have shown, however, that mammograms are effective in detecting early breast cancer in this group of relatively young women with dense breasts (11–13). Lung cancer is another one of the most common second malignancies after Hodgkin's disease. The role of chest CT screening in high-risk patients based on smoking history is currently being studied in the general population in a prospective randomized trial conducted by the United States National Cancer Institute (14). Due to reasons outlined above, it is unlikely that such a study will be conducted in survivors of Hodgkin's disease. A decision analysis addressing this question has been performed and the results were presented at the workshop. The performance of annual low-dose chest CT in patients 5 yr or more after mediastinal radiation therapy for Hodgkin's disease yielded a survival gain that was comparable to other well-accepted cancer screening strategies (15). It was also highly cost-effective, especially among survivors who were also smokers, due to the multiplicative effect of tobacco use on treatment-related lung cancer risk.

Recommendations: Although there are no prospective data quantifying the benefit of screening mammography in this patient population, given the increased risk and well-described risk factors for breast cancer after Hodgkin's disease, the group recommended screening female patients irradiated before the age of 35 when at least a portion of the breast was in the treatment field. Annual mammography screening was recommended starting at the latest 8 yr following irradiation, or when the patient reaches age 40, whichever occurs earlier. Women should also be encouraged to perform monthly self-breast examination and yearly breast examination by a health care professional.

The group recommended that any use of hormone replacement therapy in postmenopausal women treated for HD be carefully reviewed, given

recent findings of the increased risk of breast cancer and cardiovascular disease from estrogen replacement therapy in the general population (16–19). The convincing evidence of hormonal influence on breast cancer risk in young women treated for Hodgkin's disease warrants further study before management strategies can be recommended for those with treatment-related premature menopause (7, 20). In their own clinical practices, some workshop participants prescribe low-dose hormone replacement therapy to ameliorate the untoward effects of premature menopause in selected patients, and some participants also recommend avoidance of synthetic progestins in these patients given the evidence of increased breast cancer risk with combined estrogen and synthetic progestin use (19).

In view of the significantly increased lung cancer risk especially among survivors who are tobacco users (6, 21), and the poor prognosis associated with lung cancer after Hodgkin's disease (22, 23), survivors who continue to smoke should be aggressively enrolled into smoking cessation program. Only modeling data are available on the role of annual low-dose spiral chest CT as a screening strategy for lung cancer, but it should be considered in survivors who have a significant tobacco history.

Until more data are available, initiation of chemoprevention outside of a clinical trial is not recommended, since the efficacy of the agents in reducing the risk of treatment-induced as opposed to *de novo* cancers is unclear. The toxicity profile of the chemoprevention agents in the survivor population may also be different and need to be better defined.

Research priorities: The role of breast MRI screening has been studied in other high-risk women and appears to provide a greater positive predictive value than mammography (24, 25), but data are not available in survivors of Hodgkin's disease. It is a relatively non-invasive procedure, and whether breast MRI is effective in detecting additional early lesions that are missed by mammography in these patients should be evaluated prospectively. However, it needs to be weighed against the cost, as well as the anxiety and discomfort associated with false-positive findings and repeated biopsies. Costs and quality of life should therefore be included as endpoints in such a study.

With the recent compelling evidence on the influence of estrogen exposure to the risk of breast cancer after Hodgkin's disease (7, 20), the concept of the use of selective estrogen receptor modulators (SERMs) in these patients remains attractive. The low accrual in the feasibility study that was presented on tamoxifen as chemoprevention appeared to be due largely to the perceived significant side effects of tamoxifen. Other SERMs are available with different risk and benefit profile that may potentially be more appealing to this population. Specifically, raloxifene, currently being compared against tamoxifen as chemoprevention in the normal population, may be a potential agent, as it does not appear to be associated with an increased risk of endometrial cancer (26). However, raloxifene use is currently limited to only postmenopausal women and its long-term safety still needs to be confirmed.

One area of research that has not been revealing thus far is in the search of molecular markers that may predict for second malignancy development (27, 28). Establishing a multi-institutional blood and tissue bank and collaboration with molecular biologists are essential in the advancement of this field of research. The identification of patients with increased genetic susceptibility to treatment-related cancer may have important implications in the initial treatment design as well as follow-up programs after treatment. More importantly, it may ultimately help in the development of molecularly targeted preventive treatment in the affected patients.

Cardiac disease

Summary of data presented: Data from Stanford, Harvard, cancer centers in Amsterdam and Rotterdam and the SEER program were presented on the excess mortality due to cardiac disease in patients treated for Hodgkin's disease (2–4). The incidence and range of, and risk factors for cardiac morbidity in survivors of Hodgkin's disease were also presented based on studies conducted at Stanford, Princess Margaret Hospital, Toronto Sunnybrook Regional Cancer Center, the University of Rochester, and the Childhood Cancer Survivor Study (CCSS) Group (29–31). Key observations include:

(i) The excess risk of mortality from cardiac disease is significantly increased after approximately 10 yr from treatment, and appears to increase with follow-up time.
(ii) Coronary heart disease account for the majority of cardiac mortality.
(iii) Other cardiac morbidities included: valvular disease, pericardial disease, ventricular dysfunction and conduction abnormalities.
(iv) The risk of coronary heart disease, valvular disease and ventricular dysfunction (wall motion abnormalities and/or reduced left ventricular mass) increase with increasing latency since treatment.
(v) Radiation exposure is the main treatment-related risk factor; there does not appear to be evidence suggesting that doxurubicin (at doses

given for Hodgkin's disease) increases the risk of cardiac disease. However, more data are needed in both the pediatric and adult populations.

Despite the wide range of cardiac complications after Hodgkin's disease therapy, only limited data are available on the role of screening and early intervention. Results of a recently completed prospective cardiac screening study from Stanford on survivors of Hodgkin's disease were presented at the workshop. In this study, survivors underwent lipid testing, resting and stress echocardiogram and electrocardiogram (ECG), and radionuclide perfusion imaging. Patients with abnormal imaging underwent angiography. The sensitivity of stress ECG, stress echocardiogram and perfusion studies in predicting 50% or more of coronary stenosis based on the angiography findings were 38%, 59%, and 65%, respectively. The screening yield appeared to be greater at 10 yr or more after treatment. Valvular abnormality was detected in a high proportion of patients especially in those beyond 10 yr from treatment, and in the majority of the cases, they were not picked up by auscultation. Part of the results of this screening study has been published since the workshop (29).

Recommendations: The group agreed that the increased long-term risk of cardiac disease and it's adverse impact on survival justify the performance of non-invasive cardiac screening studies such as resting and stress echocardiogram in patients who are 10 yr or more out from treatment. The specific types of tests to be performed, timing and frequency are unclear and need to be refined and tailored to individual patients. Because of the unique nature of the cardiac abnormalities seen in this population, patients may benefit from at least an initial evaluation by a cardiologist with experience in the care of cancer survivors. Enrolling patients on existing trials evaluating the role of cardiac screening in survivors of Hodgkin's disease, if available, is strongly encouraged, so that more data can be gathered on this important subject.

It was also discussed at the workshop the role of screening for modifiable cardiac risk factor in this population. Subsequent to the workshop, there have been further data demonstrating the contribution of traditional cardiac risk factors to the risk of cardiac disease after Hodgkin's disease (32, 33). It is recommended that survivors be screened and aggressively treated for existing cardiac risk factors such as hypertension, hypercholesterolemia and diabetes mellitus. Smokers should be referred to smoking cessation program. In addition, survivors should be encouraged to engage in regular exercise and to follow a healthy diet. As discussed, such risk factor screening and intervention should ideally be performed as part of a trial if one is available.

Research priorities: Data presented at the workshop has prompted the initiation of a cardiac screening study with incorporation of quality of life in survivors of Hodgkin's disease at the Dana-Farber Cancer Institute. This ongoing study, which thus far has an enrollment rate of over 95%, will hopefully clarify the feasibility and yield of cardiac screening for survivors of Hodgkin's disease, the relative contribution of treatment-related and other traditional cardiac risk factors to the risk of cardiac disease, and the impact of cardiac complications on patients' quality of life. Other prevention strategies include the use of angiotensin-converting enzyme inhibitors, and from the initial treatment standpoint, the use of cardioprotective agents during treatment. These are potential areas to be considered for future research.

Recent advances in radiation therapy planning and treatment have allowed more accurate dose determination to specific structures and more targeted dose delivery. A work-in-progress study at the University of Rochester was presented at the workshop evaluating the dose-volume histograms of individual cardiac structures in patients receiving mediastinal irradiation. Such research efforts may enhance our understanding of the dose-response relationship for various types of cardiac complications and guide radiation oncologists in their radiation treatment design.

Other late effects (infection, pulmonary, endocrine, and quality of life)

Summary of data presented: Data on the risk of sepsis, implications for vaccination and prophylactic antibiotic practice, and the current Center for Disease Control and Prevention (CDC) guidelines on management of splenectomized patients were presented (34–36). Data on antibody responses to vaccination in patients who have been treated for Hodgkin's disease were also reviewed (37–39). The Stanford group presented their data on the excess mortality from infectious causes and pulmonary toxicity after Hodgkin's disease (2). Preliminary results from the CCSS questionnaire study on the incidence and spectrum of self-reported pulmonary disease, thyroid abnormalities, infertility and mental distress of survivors of childhood Hodgkin's disease were presented. Preliminary results of a Harvard questionnaire study modeled after the CCSS study but conducted mostly in adult survivors were also presented. Below summarizes the data that were reviewed:

(i) Infectious and pulmonary causes both contribute to the excess mortality of survivors of Hodgkin's disease, although to a much lower extent than second malignancy and cardiac disease.
(ii) Overwhelming sepsis in asplenic patients represents the leading cause of infectious death.
(iii) Abnormal pulmonary function is found in up to 30% of long-term survivors.
(iv) Abnormal thyroid function (mostly hypothyroidism) is reported in about 50% of the long-term survivors.
(v) Sterility is an important concern for young adults treated for the disease, and continues to affect some of the newly diagnosed patients treated with newer, more aggressive regimens [e.g. bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP)].
(vi) Long-term survivors continue to report increased fatigue years after treatment and late medical complications of Hodgkin's disease therapy may contribute to the fatigue.

Recommendations: According to guidelines from the CDC, routine vaccination against encapsulated organisms in patients with functional or anatomical asplenia is recommended. Our strongest recommendation is for pneumococcal polysaccharide vaccine. Fewer data are available on the role of meningococcal polysaccharide vaccine and Haemophilus influenza type B vaccine, but a number of centers are recommending all three vaccinations to be given every 5–6 yr. Given the lack of data supporting it's utility, we do not recommend the use of prophylactic antibiotics in these patients.

Routine pulmonary function testing in asymptomatic survivors is likely of limited value. However, in patients reporting such respiratory symptoms as chronic and/or progressive shortness of breath, dyspnea on exertion, persistent cough or recurrent pneumonia, it is appropriate to obtain baseline pulmonary function testing and imaging studies, and also consider referral to pulmonologists for further evaluation.

For patients who have received radiation therapy to the upper mediastinum and neck region, obtaining thyroid stimulating hormone levels during follow-up visits is recommended. A careful thyroid examination with attention to enlargement or nodules should also be performed as part of the physical examination.

Part of the 2004 American Society of Clinical Oncology Educational Course on risks of infertility and ways to preserve fertility after cancer therapy stemmed from presentations and discussions at the Bellagio workshop (40). Newly diagnosed patients who are interested in preserving fertility should be counseled on options of sperm cryopreservation, and cryopreservation of oocytes or embryos. In patients with difficulty conceiving after Hodgkin's disease therapy, early referral to a reproductive endocrinologist with an expertise on managing cancer survivors is recommended. Patients with permanent gonadal failure may benefit from being provided with information on and access to donor, surrogacy or adoption programs.

Research Priorities: For infectious complications, the group concluded that the magnitude and range of infectious risks in patients, who are treated with the newer, more intense chemotherapy needs to be clarified (41). There is currently also a lack of data on the types of infections that survivors of Hodgkin's disease are at risk for in developing countries, especially for infections that are more endemic outside of the developed world, and this needs to be addressed as the number of long-term survivors increase in different parts of the world.

There is a need to prospectively document the pulmonary toxicity associated with the newer, more dose intense regimen that consist of a variety of chemotherapeutic agents, including Stanford V and BEACOPP (41, 42). Additional work is also needed in identifying risk factors for chronic lung injury after Hodgkin's disease therapy, including smoking history, preexisting lung disease, recurrent pneumonia, family history of lung disease and genetic predisposition. Translational research work on the molecular mechanism of pulmonary fibrogenesis may be valuable, and may allow development of targeted drug therapy that reduces lung damage both during and after Hodgkin's disease treatment.

Current randomized studies testing the safety and effectiveness of administration of gonadotropin-releasing hormone agonist during Hodgkin's disease chemotherapy to minimize follicle depletion, undertaken by two European Groups (Belgium and GHSG), were discussed. The clinical experience on oocyte, follicle, or ovarian tissue, as well as testicular tissue cryopreservation is still limited (43, 44). Collaboration with reproductive endocrinologists in testing its efficacy will broaden the reproductive options of patients.

Continued research efforts in correlating fatigue with other prevalent long-term sequelae of Hodgkin's disease therapy may strengthen the role of fatigue screening, as it may help in early discovery and intervention of physical abnormalities. In addition to clinical factors, the contribution of non-clinical factors such as demographic profile and socioeconomic status to fatigue and reduced quality of life needs to be evaluated, as it may allow identification of subsets of vulnerable patients who

may benefit from additional support. Prospectively designed interventional strategies to ameliorate fatigue (e.g. exercise, cognitive behavioral therapy) in these patients may also be of value.

Treatment reduction

Summary of data presented: Ongoing trials and recently completed trials investigating treatment reduction, largely in patients with early stage disease were presented. The main strategies included limiting the number of cycles of chemotherapy, eliminating specific drugs from the ABVD regimen, reducing the radiation dose, further reducing the involved-field, and eliminating radiation therapy. Areas of investigation and some of the available results are outlined as follows:

(i) Preliminary results of the GHSG HD 10 trial comparing two or four cycles of ABVD followed by 20 or 30 Gy of involved-field radiation therapy were presented. The results have also been presented in abstract form since the workshop (45). No difference between the four arms has been detected, although the follow-up (2 yr) is too short for any conclusions at this time.

(ii) An ongoing GHSG trial, HD 15, is comparing ABVD, AVD, ABV, and AV, all followed by 30 Gy of involved-field radiation therapy.

(iii) Results of a randomized trial from Tata Memorial Hospital (results had been published since the workshop) comparing six cycles of ABVD followed by involved field irradiation with ABVD alone showed a significant disease-free and overall survival decrement with the omission of radiation therapy (46).

(iv) In an ongoing EORTC H9F trial, comparing EBVP II followed by 36 or 20 Gy of involved-field irradiation or no further treatment, the chemotherapy alone arm was closed early due to an unacceptably high relapse rate. The preliminary results have been presented in abstract form since the workshop (47).

(v) The EORTC is currently investigating further limiting the traditional definition of involved-field from irradiation of entire nodal groups to treatment of only the affected lymph nodes.

Recommendations: The group agreed that in general, treatment reduction should be limited to patients with early stage, favorable-prognosis disease, since the priority in patients with unfavorable or advanced-stage disease continues to be improving the cure of Hodgkin's disease. Four cycles of ABVD followed by involved-field radiation therapy is currently still considered the standard of treatment for early stage disease. The group concluded that a dose beyond 30 Gy is unnecessary for patients with an adequate response to chemotherapy. Until more data are available, the use of less chemotherapy, lower doses or smaller fields of radiation therapy, or treatment with chemotherapy alone should only be done as part of a trial in which patients will be carefully followed.

Future research priorities: As outlined above, a number of treatment reduction strategies are being investigated. Recent technological advances in radiation planning and delivery may allow more conformal targeting and sparing of normal tissue in selected cases. Furthermore, the pathogenesis and biology of Hodgkin's disease are currently being actively explored (48). The elucidation of the molecular mechanism of Hodgkin's disease development may provide molecular targets for the treatment of the disease and may reduce the need to use traditional cytotoxic therapy. As new treatment approaches are developed and studied, one of the challenges is maintaining follow-up of patients, since at least 10–15 yr follow-up time is needed to fully appreciate the late effects. Novel ways need to be developed to track patients and to ensure continued long-term follow-up of trial participants.

Although a detailed analysis is beyond the scope of this document, the workshop identified numerous impediments to the follow-up of patients after Hodgkin's disease in developing countries including the high morbidity and mortality from infectious disease, and limited access to medical care, training, and education. The potential value of an international consortium that focused on improving clinical practice and research in late effects in Hodgkin's disease was discussed. Both professionals and survivors of Hodgkin's disease who are concerned with late effects in Hodgkin's disease could be invited to join the consortium. The group proposed that the World Wide Web might be an ideal medium in the development of the consortium, which may provide a means globally to enhance research and to improve clinical care.

References

1. Cosset JM, Henry-Amar M, Meerwaldt JH. Long-term toxicity of early stages of Hodgkin's disease therapy: the EORTC experience. EORTC Lymphoma Cooperative Group. Ann Oncol 1991;**2** (Suppl. 2):77–82.
2. Hoppe RT. Hodgkin's disease: complications of therapy and excess mortality. Ann Oncol 1997;**8**:115–118.
3. Ng AK, Bernardo MP, Weller E, *et al*. Long-term survival and competing causes of death in patients with early-stage Hodgkin's disease treated at age 50 or younger. J Clin Oncol 2002;**20**:2101–2108.
4. Aleman BM, van den Belt-Dusebout AW, Klokman WJ, Van't Veer MB, Bartelink H, van Leeuwen FE.

Long-term cause-specific mortality of patients treated for Hodgkin's disease. J Clin Oncol 2003;**21**:3431–3439.
5. Dores GM, Metayer C, Curtis RE, *et al*. Second malignant neoplasms among long-term survivors of Hodgkin's disease: a population-based evaluation over 25 years. J Clin Oncol 2002;**20**:3484–3494.
6. Travis LB, Gospodarowicz M, Curtis RE, *et al*. Lung cancer following chemotherapy and radiotherapy for Hodgkin's disease. J Natl Cancer Inst 2002;**94**:182–192.
7. Travis LB, Hill DA, Dores GM, *et al*. Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. JAMA 2003;**290**:465–475.
8. Diller L, Mauch P, Medeiros-Nancarrow C, *et al*. A feasibility study of tamoxifen chemoprevention in Hodgkin's disease (HD) survivors. J Clin Oncol ASCO Annual Meeting Proceedings (Post-Meeting Edition), 2004;**22** (Suppl. 15):8551.
9. Allen M, Ng A, Mauch P, *et al*. A decision and cost-effectiveness analysis on tamoxifen as chemoprevention for breast cancer in young women treated with radiation therapy for Hodgkin's disease. ASTRO Abstr 2002. Int J. Radiat Oncol Biol Phys 2002;**54** (suppl. 1):11.
10. Fisher B, Costantino JP, Wickerham DL, *et al*. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 1998;**90**:1371–1388.
11. Yahalom J, Petrek JA, Biddinger PW, *et al*. Breast cancer in patients irradiated for Hodgkin's disease: a clinical and pathologic analysis of 45 events in 37 patients. J Clin Oncol 1992;**10**:1674–1681.
12. Wolden SL, Hancock SL, Carlson RW, Goffinet DR, Jeffrey SS, Hoppe RT. Management of breast cancer after Hodgkin's disease. J Clin Oncol 2000;**18**:765–772.
13. Diller L, Medeiros Nancarrow C, Shaffer K, *et al*. Breast cancer screening in women previously treated for Hodgkin's disease: a prospective cohort study. J Clin Oncol 2002;**20**:2085–2091.
14. National Lung Screening Trial. http://www.cancer.gov/nlst.
15. Das P, Ng A, Earle C, *et al*. Decision analysis on computed tomography screening for lung cancer in Hodgkin's disease survivors. ASCO Abstr 2003. Int J. Radiat Oncol Biol Phys 2003;**57**(Suppl. 1):5213.
16. Chlebowski RT, Hendrix SL, Langer RD, *et al*. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. JAMA 2003;**289**:3243–3253.
17. Manson JE, Hsia J, Johnson KC, *et al*. Estrogen plus progestin and the risk of coronary heart disease. N Engl J Med 2003;**349**:523–534.
18. Rossouw JE, Anderson GL, Prentice RL, *et al*. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA 2002;**288**:321–333.
19. Fournier A, Berrino F, Riboli E, *et al*. Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort. Int J Cancer 2004;**114**: 448–454.
20. van Leeuwen FE, Klokman WJ, Stovall M, *et al*. Roles of radiation dose, chemotherapy, and hormonal factors in breast cancer following Hodgkin's disease. J Natl Cancer Inst 2003;**95**:971–980.
21. van Leeuwen FE, Klokman WJ, Stovall M, *et al*. Roles of radiotherapy and smoking in lung cancer following Hodgkin's disease. J Natl Cancer Inst 1995; **87**:1530–1537.
22. Ng AK, Bernardo MV, Weller E, *et al*. Second malignancy after Hodgkin disease treated with radiation therapy with or without chemotherapy: long-term risks and risk factors. Blood 2002;**100**:1989–1996.
23. Das P, Ng A, Stevenson M, *et al*. Clinical Course of Thoracic Cancers in Hodgkin's Disease Survivors. Ann Oncol 2005;**16**:793–797.
24. Kriege M, Brekelmans CT, Boetes C, *et al*. Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. N Engl J Med 2004;**351**:427–437.
25. Bluemke DA, Gatsonis CA, Chen MH, *et al*. Magnetic resonance imaging of the breast prior to biopsy. JAMA 2004;**292**:2735–2742.
26. Johnston CC, Jr, Bjarnason NH, Cohen FJ, *et al*. Long-term effects of raloxifene on bone mineral density, bone turnover, and serum lipid levels in early postmenopausal women: three-year data from 2 double-blind, randomized, placebo-controlled trials. Arch Intern Med 2000;**160**:3444–3450.
27. Nichols KE, Levitz S, Shannon KE, *et al*. Heterozygous germline ATM mutations do not contribute to radiation-associated malignancies after Hodgkin's disease. J Clin Oncol 1999;**17**:1259.
28. Broeks A, Russell NS, Floore AN, *et al*. Increased risk of breast cancer following irradiation for Hodgkin's disease is not a result of ATM germline mutations. Int J Radiat Biol 2000;**76**:693–698.
29. Heidenreich PA, Hancock SL, Lee BK, Mariscal CS, Schnittger I. Asymptomatic cardiac disease following mediastinal irradiation. J Am Coll Cardiol 2003;**42**:743–749.
30. Hodgson DC, MacKenzie RG, Forde N, *et al*. Cardiac toxicity following modern treatment for hodgkins disease: Impact of combined modality treatment with doxorubicin and mediastinal radiation therapy. Int J Radiat Oncol Biol Phys 2004;**60**:S216.
31. Grenier MA, Lipshultz SE. Epidemiology of anthracycline cardiotoxicity in children and adults. Semin Oncol 1998;**25**:72–85.
32. Hull MC, Morris CG, Pepine CJ, Mendenhall NP. Valvular dysfunction and carotid, subclavian, and coronary artery disease in survivors of hodgkin lymphoma treated with radiation therapy. JAMA 2003;**290**:2831–2837.
33. Strasser JF, Li S, Neuberg D, *et al*. Late cardiac toxicity after mediastinal radiation therapy for Hodgkin's disease. Int J Radiat Oncol Biol Phys 2004;**60**:S217.
34. CDC. Prevention pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1997;**46**:1–24.
35. CDC. Prevention and control of meningococcal disease and meningococcal disease and college students: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2000;**49**:1–20.
36. CDC. Haemophilus b conjugate vaccines for prevention of Haemophilus influenzae type b disease among infants and children two months of age and older: recommendations of the Immunization Practices Advisory Committee (ACIP). MMWR 1991;**40**:1–7.
37. Minor DR, Schiffman G, Mc Intosh LS. Response of patients with Hodgkin's disease to pneumococcal vaccine. Ann Intern Med 1979;**90**:887–892.
38. Molrine DC, George S, Tarbell N, *et al*. Antibody responses to polysaccharide and polysaccharide-conjugate vaccines after treatment of Hodgkin disease. Ann Intern Med 1995;**123**:828–834.
39. Chan CY, Molrine DC, George S, *et al*. Pneumococcal conjugate vaccine primes for antibody responses to polysaccharide pneumococcal vaccine after treat ment of Hodgkin's disease. J Infect Dis 1996;**173**:256–258.
40. Carde P. Risks Of Infertility And Early Menopause From Anticancer And Immunosuppressive Programs: Methods

Of Fertility Preservation And Palliation. New Orleans, LA, USA: American Society of Clinical Oncology Educational Book, 2004: 400–417, (ISSN 1524-8748).
41. Diehl V, Franklin J, Pfreundschuh M, *et al*. Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease. N Engl J Med 2003;**348**:2386–2395.
42. Horning SJ, Hoppe RT, Breslin S, Bartlett NL, Brown BW, Rosenberg SA. Stanford V and radiotherapy for locally extensive and advanced Hodgkin's disease: mature results of a prospective clinical trial. J Clin Oncol 2002;**20**:630–637.
43. Damani MN, Master V, Meng MV, *et al*. Postchemotherapy ejaculatory azoospermia: fatherhood with sperm from testis tissue with intracytoplasmic sperm injection. J Clin Oncol 2002;**20**:930–936.
44. Donnez J, Dolmans MM. Livebirth after cryopreserved ovarian tissue autotransplantation. Lancet 2004;**364**:2092–2093.
45. Diehl V, Brilliant C, Engert A, *et al*. Reduction of combined modality treatment intensity in early stage Hodgkin's lymphoma, interim analysis of HD10 trial of GHSG. Eur J Haematol 2004;**73**:E03a.
46. Laskar S, Gupta T, Vimal S, Muckaden MA, Saikia TK, Pai SK, Naresh KN, Dinshaw KA. Consolidation radiation after complete remission in Hodgkin's disease following six cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine chemotherapy: is there a need? J Clin Oncol 2004;**22**:62–68.
47. Thomas J. Six cycles of EBVP followed by 36Gy involved-field irradiation vs. no irradiation in favourable supradiaphragmatic clinical stages I-II Hodgkin's Lymphoma: the EORTC-GELA strategy in 771 patients. Eur J Haematol 2004;**73**:E0.
48. Diehl V, Stein H, Hummel M, Zollinger R, Connors JM. Hodgkin's lymphoma: biology and treatment strategies for primary, refractory, and relapsed disease. Hematol (Am Soc Hematol Educ Program) 2003;225–247.